ETHIOPIAN FOOD AND DRUG AUTHORITY

Guideline for Temporary Market Authorization of Medicinal Gases

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Seble Shambel

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1. Introduction

Medicinal gases play a critical role in modern healthcare, serving as essential therapeutic agents for various medical conditions. They comprise of medicinal products / drugs that are supplied as a gas or gas mixtures. Medical gasses whose mode of action is achieved primarily based on pharmacological, immunological or metabolic action in/on the body are classified as a medicinal gas. Therapeutic gases include Oxygen, Nitrogen, Nitrous oxide(N_2O), mixture of nitrous oxide and oxygen, Nitric oxide (NO), Mixture of Nitric oxide with oxygen, Carbon oxide, mixture of carbon dioxide with oxygen, medical air (consisting largely of NMT 23.5% oxygen and NLT 19.5% nitrogen) and Helium, mixture of helium with oxygen. Gases designated for therapeutic purpose must undergo rigorous testing and meet standards before use. On the other hand, gases or gas mixtures in which mode of action is achieved primarily by physical in nature and not achieved primarily based on pharmacological, immunological or metabolic action in/on the body, such as gases for insufflations of the abdominal cavity for laparoscopy and gases for removal of warts (e.g. liquid nitrogen) are classified as medical device.

Medicinal gases, like other medicinal products, are required to have a Marketing Authorization (product license) to be sold or used in the healthcare facilities. According to article 20(2) of the Food and Medicine Administration Proclamation No. 1112/2019, product registration and marketing authorization shall be granted after assessing the quality, safety and efficacy of medicines with the exception of compelling circumstance. Therefore, to get marketing authorization approval and use medicinal gasses, dossier assessment and endorsement is one of a prerequisite for marketing medicinal gasses. This guideline, containing abbreviated market authorization requirement, has been developed to provide a clear requirement for the registration, marketing authorization, and ongoing regulation of medicinal gases. It is designed to ensure that all medicinal gases available in the market are safe for use, of high quality, and effective for their intended purposes.

The guideline is developed by the authority to issue temporary market authorization for medicinal gasses by considering the current status of medicinal gasses manufacturers. Full authorization will be granted gradually by evaluating the manufacturers' cGMP compliance levels. This authorization (MA) covers the medical gasses and its primary packing (container

including the valve). A valve/built-in pressure regulator assembly that cannot be separated from the cylinder is also part of the MA.

2. Definition

a) **Medicinal gases:** gases or gas mixtures intended for the administration to patients for therapeutic purpose such as anesthetic, therapeutic, prophylactic and diagnostic use.
b) **Medicinal gas finished product:** gases that has undergone all stages of production and quality control, including packaging in its final container and labeling.
c) **Compressed gas**: Gas which, when packaged under pressure for transport, is entirely gaseous at all temperatures above –50°C.
d) **Container**: A container is a cryogenic vessel (tank, tanker or other type of mobile cryogenic vessel) a cylinder, a cylinder bundle or any other package that is in direct contact with the gas.
e) **Cryogenic gas**: A gas which liquefies at 1.013 bar at temperatures below –150°C.
f) **Cylinder**: Container usually cylindrical suited for compressed, liquefied or dissolved gas, fitted with a device to regulate the spontaneous outflow of gas at atmospheric pressure and room temperature.
g) **Gas**: Any substance that is completely gaseous at 1.013 bar and +20°C or has a vapour pressure exceeding 3 bar at +50°C.
h) **Hydrostatic pressure test**: Test performed as required by national or international regulations, in order to ensure that pressure containers are able to withstand pressures up to the container's design pressure.
i) **Liquefied gas**: A gas which, when packaged for transport, is partially liquid (or solid) at a temperature above $-50^{O}C$.
j) **Cylinder Bundle**: an assembly of cylinders, which are fastened together in a frame and interconnected by a manifold, transported and used as a unit.
k) **Filling Ratio**: Relationship between the weight of gas introduced into a container and the weight of water at room temperature that will fill the same container ready for use.

3. Scope

This guideline is applicable to any gas or any mixture of gasses intended to be used for or presented in anyway as appropriate for:

- Curing or preventing disease, deficiencies, wounds or pain in humans
- Making medical diagnosis in humans or
- Restoring, improving or otherwise modifying physiological functions in humans by exerting pharmacological, immunological or metabolic effect.

This guideline is not applicable for:

i) Gases classified as medical devices;

ii) Gases used for animal use (veterinary), cosmetic/aesthetic purpose, laboratory purpose (e.g., gas for freezing of tissue samples, calibration gas), Recreational gases (e.g., oxygen gas for diving, mountain climbing) and Industrial purposes;

iii) Gases produced *in situ* in hospitals (i.e manufacturing processes undertaken in or by the hospitals and home care containers of gases) and

iv) Devices and accessories used as containers for gasses and for delivery of the gasses to the patients. (eg. Empty cylinder, pressure regulator and pipe network).

4. Requirements for temporary marketing authorization

Risk-based dossier assessment approach is one of the strategic directions of the regulatory authority to expedite marketing authorization process. This requires classification of products in to low and high-risk category so as to proportionate risks during dossier assessment.

For low-risk medicines, the evaluation process will be limited to a 'partial review of the product dossier, concentrating on the assessment of administrative requirements, product information, specifications, stability and shelf life, and others as applicable. Since, medicinal gasses currently manufactured locally has been used for the proposed indications and administered route or more than 10 years their safety and efficacy are well documented in scientific literatures such products can be authorized by evaluating limited documents submitted by applicants.

4.1. Administrative and Product Information

The below abbreviated lists of documents and requirements are based on the requirements for Module 1 of medicine registration guidelines of EFDA.

a) Covering Letter

Dated and signed letter for submission of the dossier by mentioning the product.

b) Application Form

The applicant should complete application online on the eRIS system (https://www.eris.efda.gov.et/login) through low-risk medicine application pathway.

The applicant should also upload filled and signed scanned copy of application form provided in Annex I of this document.

c) Manufacturing license(competency certificate)

A Copy of valid Manufacturing license certificate and commitment letter to fully comply for medicinal gasses GMP requirements.

d) Product information

Summarized product information including the safety rules and special conditions of storage, transport and utilization shall be provided in the SmPC along with packaging slip and labeling plans.

Such information shall be uploaded on the eRIS(https://www.eris.efda.gov.et/) through low-risk medicine application pathway.

e) Upload copy of service fee payment receipt

4.2. Finished Drug Product (Medicinal Gas)

4.2.1 Description and Composition of the Drug Product

1) The applicant should describe the composition of medicinal gas or mixture of gasses. This should include the type of active substances or a mixture of active substances and gaseous excipients.

2) In the cases of Mixtures, that consists of one or more active substances, or one active substance diluted in a gaseous excipient the applicant should:

a) Describe the percentage formula (v/v) and the deliverable volumes with tolerable deviations.

b) Specify the density or the compressibility factor for each gas and for the mixture under standard conditions (15^{o}C, 1 atm) as scientific data.

c) Provide the data that makes it possible to establish the relationship between concentration values expressed as pressure (15^{0}C), volume (15^{0}C, 1 atm) and weight.

3) For each gas, the application should include details of:

a) The physical state;

b) the pressure of compressed gases (15oC);

c) The type of container and;

d) The concentration of the active substance.

Note: Containers that have different types of valves can be included in the same application.

4) The name of the medicinal gas should be in agreement with the EFDA recognized Pharmacopoeia monograph and should contain at least the following information:

a) name of the gas followed by medicinal or invented name;

b) physical form of the product;

c) name of manufacturer;

d) pressure and/or concentration;

e) gas for inhalation and;

f) Others as applicable.

Note: Cylinder or cylinder bundle, Mobile evaporator/mobile cryogenic container, Fixed evaporator/fixed cryogenic containers may be included in the same MA application.

4.2.2. Manufacture

1) The name of the gas, followed by the word medicinal must be systematically used from the time the manufacturer designate that the finished product is for medicinal purpose. When feasible, dedicated tanks should be used for the purpose of manufacture of medicinal gas.
2) Manufacture consists of the operations of division or distribution and filling into dedicated pharmaceutical and medicinal packaging. Packaging is often automated and may include prior modification of the physical state of the gas (vaporization by heating of liquefied gas and compression). It may also include one or several successive mixing operations (by weight or nanometrically, with or without homogenization).
3) A detailed diagram of the manufacturing process should be presented, together with the controls carried out at the different critical stages.
4) The production station that supplies each filling area is indicated.
5) The automated packaging system or mixing systems and the specification of the equipment (pumps, balances, etc) should be described.

4.2.3. Process Validation and/or Evaluation

1) The applicant should provide process validation and or evaluation report performed based on the type of cylinder and /or gas by using suitable validation techniques.

a) For cylinders of single gases

i. Validation of the cylinder filling process should be performed by a weighing *(or double weighing)* control, including the calculation of the mean, standard deviation and coefficients of variation, or by pressure if justified.

ii. Validation can be also performed by determining the amount of gas contained in a cylinder compared with a reference cylinder filled with the charge of gas to avoid the problems of fluctuations in pressure as a function of temperature.

iii. The reproducibility of filling is also verified whatever the composition of the finished product batch *(homogenous or heterogeneous).*

iv. For compressed gases, the temperature and pressure stabilization time after filling which depends upon various capacities, nature of material, thermal exchange, ambient temperature (and any variation in it during the stabilization time), rate of filling of the cylinder, airflow over the cylinder and its proximity to any adjacent filled cylinders should be specified, unless otherwise justified.

v. The integrity of the filling system to indicate leak tightness to prevent possible contamination of the system under vacuum or an estimate of the yield accounted for losses as an annual average should be provided.

vi. The tolerated limits of temperature and pressure should be provided (specifying especially the hydrostatic pressure test and the bursting pressure of the cylinder). On the safety level, any problems of possible overload of compressed or liquefied gas are addressed.

vii. In the case of cylinder bundles and mobile evaporators, validation of the filling procedure should also be performed by weighing or by pressure if justified.

viii. In the case of fixed evaporators, validation can consist of the absence of impurity enrichment due to the formation of degradation products with time, to trapping because of the temperature and to transfers from one container to another during the manufacturing process or during sampling. It should be specified whether the impurities remain at the same proportions between the gaseous and liquid phases as the container is emptied. The minimal threshold for filling the fixed evaporator should be specified to avoid any risk of impurity enrichment.

ix. Thus, scientific data should be provided for:

- a theoretical evaluation of the level of impurity enrichment during blowing down/filling cycles for a cryogenic container,
- an analysis of liquid phase samples (performed on the dedicated tank in the filling area or on the dedicated tank in the production station) and of gaseous and liquid phase

samples (performed on fixed hospital evaporators), supported by a comprehensive list of potential impurities.

b) For Gas Mixtures

i. In the case of mixtures, validation should concern with the manufacturing operation for the mixture considered. It should take into account all the critical parameters of the manufacturing process and especially discuss reproducibility in the case of manual cylinder-by-cylinder filling, the role of the nature of the phase and of the temperature of each gas when introduced into the cylinder and the homogenization conditions. The successive physical states of each gas and of the gas mixture during filling should be indicated. A phase diagram should be provided.

ii. Validation can also be concerned with other types of mixtures.

iii. In the case of the manufacture of an intermediate product, its validation should be carried out under the same conditions and using the same methodology.

4.2.4. Control of Drug Product

1) Specification

a) The control of the finished product should consist of the control according to the monograph in the national standard or pharmacopeia recognized by the Authority or using validated inhouse methods if shown to be equivalent.

b) The specification should at least include test for identity, assay and purity, the appearance of the cylinders, the labelling and the pressure (for cylinders and cylinder bundles).

c) All the constituents of the mixture should be identified including excipients. The different constituents of the mixture should be assayed, unless otherwise justified.

d) The control of the filling charge can be performed during packaging and the control of airtightness after filling.

2) **Analytical Procedures**

a) The applicant should provide analytical procedures to ensure that the medicinal gases produced meet the required specifications for identity, purity, assay and other required test parameters

b) The analytical methods should be validated/verified to ensure that the methods are suitable for their intended purpose and provide accurate and reliable results.

c) In the case of liquefied gases, the nature of the phase *(liquid or gaseous)* should be indicated, and the method of sampling for the control should be specified.

d) In the case of impurities that are preferentially present in the gaseous phase and eliminated to a large extent during the first drawing off *(e.g. nitric oxide in medical nitrous oxide)*, the order of analyses should be clearly specified.

e) The interval elapsed between manufacture and the control of the finished product should be indicated according to the pharmacopeia recognized by the authority.

f) In the case of gases of limited stability, it should be specified whether a second control, performed sometime after the first to detect the appearance of impurities.

3) **Batch Analyses**

a) In the case of cylinders, the batch analysis certificate should state**:**

- the batch number,
- the batch composition and size *(the batches are often heterogeneous),*
- the source of the starting materials,
- the number of the cylinder controlled,
- the capacity of the cylinder controlled,
- the value for the charge of the cylinder controlled compared to its theoretical charge so as to indicate if the analysis was performed at the start, middle or end of cylinder utilization, expressed as pressure *(compressed gas)* or weight *(liquefied gas),*
- the phase analyzed,
- the specifications and test results

- the date of analysis and the date of manufacture,
- the signature of the relevant person,
- place of manufacture

4.2.5 Container Closure System

1) The description of the containers should specify the capacity, type of material used for the container and the reference code for the manufacturer and the supplier(s) of the containers. In addition, in the case of cylinders, the type of valve and its reference code, the suppliers and the type of valve outlet connection should be stated.
2) In the case of cylinder bundles, the material and dimensions e.g., internal diameter used for the loop should be provided. This information can be provided as a table.

a) The applicant should specify the specific type of container closure system used. Medicinal gases may be packaged in a wide range of containers including:

- compressed gas cylinders,
- liquefied gas cylinders, with or without a dip tube,
- cylinder bundle,
- mobile evaporator,
- fixed evaporator,
- mobile cryogenic container,
- fixed cryogenic container.

b) The applicant should specify the reference code for the container of medicinal gas. The reference codes could be selected based on the supplier, capacity and material, particularly in the case of cylinders. For each reference and each capacity, the following information should be provided, together with the accepted deviations:

- the water capacity of the container *(in L)*,
- the amount of gaseous product released at 1atm and 15°C *(in m^3)*, and

- the weight of product stored *(in g for compressed gases or in kg for liquefied gases)*

c) The above information is necessary for compressed gas cylinders, given the variable operating pressures *(200 bar, 150 bar, etc at 15°C).*

Note: For liquefied gas cylinders, the pressure remains constant then falls suddenly at the end of use. Therefore, only the weight monitors the state of filling.

d) The filling pressure *(at 15 °C)* should be justified in comparison with the weight formula.

e) In the case of liquefied gases, the filling ratio in accordance to national and international standards and legislation should be provided so as not to exceed a maximal pressure with the risk of explosion, which can occur in the event of a change from the liquid to the gaseous or supercritical state after a temperature increase above the critical temperature.

f) The type of safety device *(valves or rupture disks)* relating to excess pressure should be specified and located *(valves or containers with pressure calibration).*

g) In the case of valves and outlets, a diagram summarizing the nature of the different constituents should be provided.

h) The method of opening the tap *(quarter turn, half-turn, progressive wheel, etc.)* the type of standardized outlet connection and the type of gasket and valve used should be specified

i) In the case of cylinders with a built-in pressure regulator, the number and the valve positions of the flow-meter and the corresponding accuracies should be documented.

j) The specific tests for the cylinders should consist in particular of gas compatibility, adiabatic compression if needs be *(oxygen)* internal and external air-tightness, endurance test, cap shock resistance, fire-resistance, valve safety, shock vibration, output precision, etc.

k) The containers should comply with the specifications of Ethiopian standard or international *(ISO)* standards concerning equipment intended to contain and deliver gases.

l) The certificate of compliance with the standards should be provided. This should include the existence of connections **(**cylinder valve outlet connection) and for the painting of the cylinder shoulder.

m) The labeling, marking, engraving and painting should be described in a detailed manner, together with a diagram of the container *(packaging plan)*. The labeling should make it clearly distinguish between cylinders for medicinal use and other cylinders *(laboratory gas, welding gas, etc.)*

4.2.6 Stability of the Finished Product

a) Stability of the finished medicinal gas should be documented

b) Specific storage conditions should be proposed by the applicant based on properties of the constituent gas.

c) In case of gases that have been used for a long time and packaged in containers that have also been used for a long time, submitting bibliographic data is sufficient.

d) Where necessary as it may be the case of gas mixtures specific shelf life should be specified by the manufacturer.

e) The influence of temperature can only be studied on small cylinders placed in special ovens and under accelerated aging conditions, on condition that they are of the same composition and fitted with the same valves and gaskets. The influence on stability of opening/closing cycles and the decrease in pressure with utilization should also be studied.

5. Post Approval Changes and Renewal Applications

5.1. Variation

a) For post approval variations, the applicants are advised to refer to and provide all relevant documents required by the guideline for submission of post approval variation medicine application as applicable.

b) Whenever a product has been withdrawn from the market for any reason the marketing authorization holder shall notify EFDA.

5.2. Renewal

Applications for renewal of marketing authorization of this category of medicines shall follow requirements specified in the latest version of Authority`s guideline for renewal of medicines marketing authorization.

6. Annex

Annex I: Application form for registration

A. Type of application (check the box applicable with the symbol ×.)			
New Application			
Renewal application			
Variation application			
B. Details on the product			
Proprietary name (trade name)			
Generic name (s) (use INN if any)			
Standard claimed (USP, BP, Ph.In, Ph. Eur., In House, etc.)			
Strength(s); percentage formula (v/v) and the deliverable volumes			
Dosage form(liquified gas or gaseous)			
Shelf life (months)			
Storage condition			
Visual Description of the product			
Description of container closure			
Packaging and pack size (type of cylinder, capacity)			
Complete qualitative and quantitative composition	Composition	Strength	Function
C. Details on the applicant			
Name			
Business address			
Telephone number			

E-mail and website address	
Contact person in a company	Name:
	Position:
	Telephone number:
	Email
Details of Finished medical gases Manufacturer site	

Signature and Stamp